1

Epidemiology of Esophageal Cancer

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This chapter reviews the epidemiology of esophageal cancer and its two major histologic types, squamous cell carcinoma of the esophagus (SCE) and adenocarcinoma of the esophagus (ACE). Although the tumors share a poor prognosis, they have rather distinct histopathologic and epidemiologic profiles. Squamous cell carcinoma of the esophagus arises from squamous epithelium that undergoes inflammatory, atrophic, and dysplastic changes whereas ACE arises through metaplastic intestinal-type changes that replace the squamous epithelium. This chapter reviews the descriptive patterns of both tumors, along with known and suspected risk or protective factors. Because ACE made up only a small fraction of esophageal cancers until recently, results from most epidemiologic studies of esophageal cancer that did not distinguish histologic types largely reflect the risk factors for SCE. Although most of the epidemiologic studies in the past have referred to SCE, special attention has recently centered on ACE in view of the rising incidence rates of this tumor.

DEMOGRAPHIC CHARACTERISTICS

Esophageal cancer is known for its marked variation by geographic region, ethnicity, and gender. In the United States, esophageal cancer accounts for only 1 percent of all diagnosed cancers; however, it is the seventh leading cause of death from cancer among men.[1] According to estimates provided by the American Cancer Society, approximately 9,200 men and 2,900 women are expected to die from esophageal cancer in the United States during 2000.[1] The lifetime risk of being diagnosed with esophageal cancer in the United States is 0.99 percent for African American men, 0.67 percent for white men, 0.43 percent for African American women, and 0.25 percent for white women.[2]

United States Mortality Patterns

Based on data from the National Center for Health Statistics, mortality rates for esophageal cancer almost doubled in the nonwhite population between 1950 and 1984, reaching a high of 14.1 per 100,000 among nonwhite men and 3.6 per 100,000 among nonwhite women (Figure 1–1). Since 1985, however, there has been a steady decrease, with rates for nonwhite men and women falling to 9.8 per 100,000 and 2.5 per 100,000, respectively, in 1995 to 1996. Mortality rates in the white population changed little during the period of 1950 to 1984, but a striking increase in rates among men occurred during the period of 1985 to 1996. Mortality rates for white men and women in 1995 to 1996 were 5.9 per 100,000 and 1.3 per 100,000, respectively. Rates specifically for African Americans (available since the early 1970s) are higher than rates for all nonwhite populations combined.

Maps showing age-adjusted mortality rates by state economic area for white Americans and African Americans during the period of 1970 to 1994 are presented in Figures 1–2 and 1–3. There were striking

differences by geographic area that are more pronounced among white Americans than African Americans and among men than women. Elevated rates for white Americans were primarily in the northeastern and mid-Atlantic states, in scattered Midwestern areas, and (females only) in the Far West. Low rates were seen among white men in the southern and Rocky Mountain states and among white women in the central portion of the country. Data for African Americans were sparse in most areas since this American population is concentrated primarily in the South and in urban areas of the East. Although patterns for African Americans are less clear than among white Americans, elevated rates for both males and females were seen in the mid-Atlantic states (including Washington, D.C.) and in coastal Georgia. From 1992 to 1996, Washington, D.C. had the highest rates for esophageal cancer among men (16.6 per 100,000) and women (3.4 per 100,000), and Utah had the lowest rates (3.4 per 100,000 among men and 0.6 per 100,000 among women).[3]

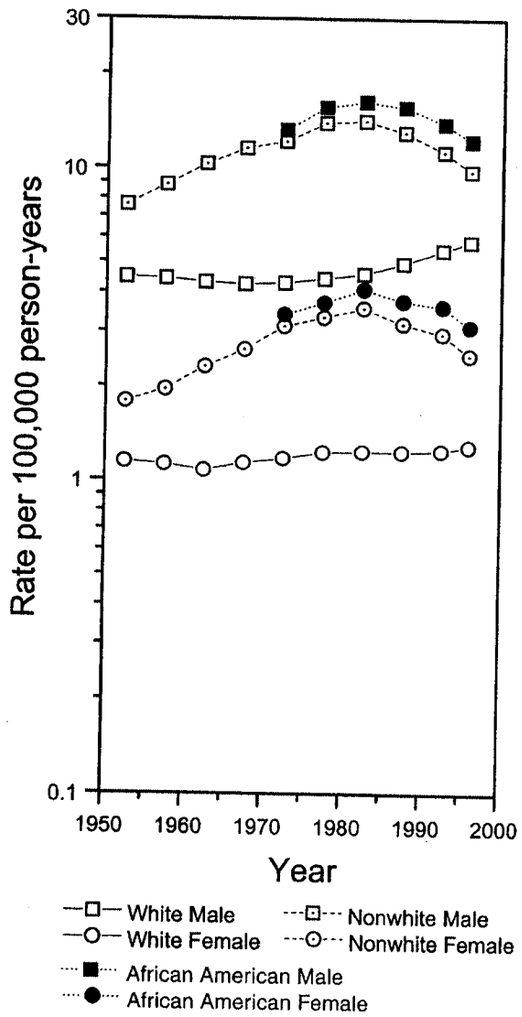


Figure 1–1. Trends in esophageal cancer mortality rates (per 100,000 person-years, age-standardized to the 1970 US population) in the United States by race and sex, 1950 to 1996. (Data from Surveillance, Epidemiology, and End Results [SEER] program, National Cancer Institute.)

United States Survival Patterns

Survival data based on follow-up of newly diagnosed cases since the 1970s are available from the Surveillance, Epidemiology, and End Results (SEER) program. Presented in this chapter are data from nine SEER population-based cancer registries surveying approximately 10 percent of the US population. Although survival among patients diagnosed with esophageal cancer is poor for all race and gender groups, significant improvements in the 5-year relative survival rates have occurred over the past two decades (Table 1–1).[2] The 5-year relative survival rates for those diagnosed during 1989 to 1995 were higher for white Americans than for African Americans (13.3% vs 8.9%) and higher for females than for males (13.1% vs 12.1%). Survival rates for those with SCE and those with ACE are similar (Table 1–2). There is a strong decreasing gradient in survival with increasing extent of disease for all esophageal cancer patients and for both SCE and ACE patients. Recent 5-year patient survival rates for all esophageal cancers have ranged from 24.9 percent (for localized disease at diagnosis) to 12.7 percent (for regional disease at diagnosis) to 1.9 percent (for distant disease at diagnosis). Although the percentage of all esophageal tumors is distributed evenly among localized, regional, distant, and unstaged tumors, a higher percentage of SCE has been localized (28%), compared with ACE (23%). A decreasing trend in survival is also observed with increasing age at diagnosis (not shown in table). For all esophageal cancer patients combined, the recent 5-year survival rates have ranged from 17.3 percent for patients < 45 years of age to 9.8 percent for patients ≥ 75 years of age.

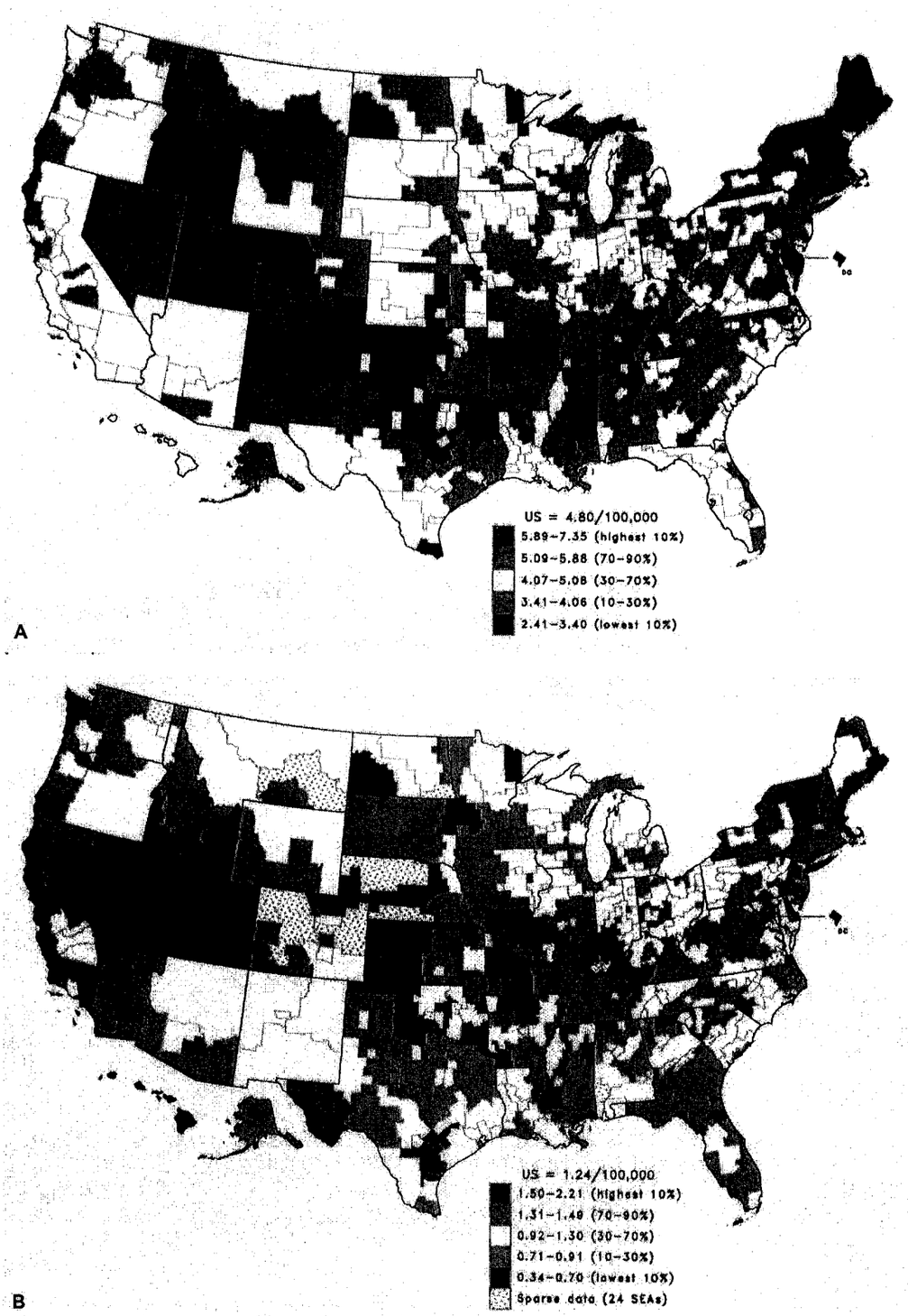
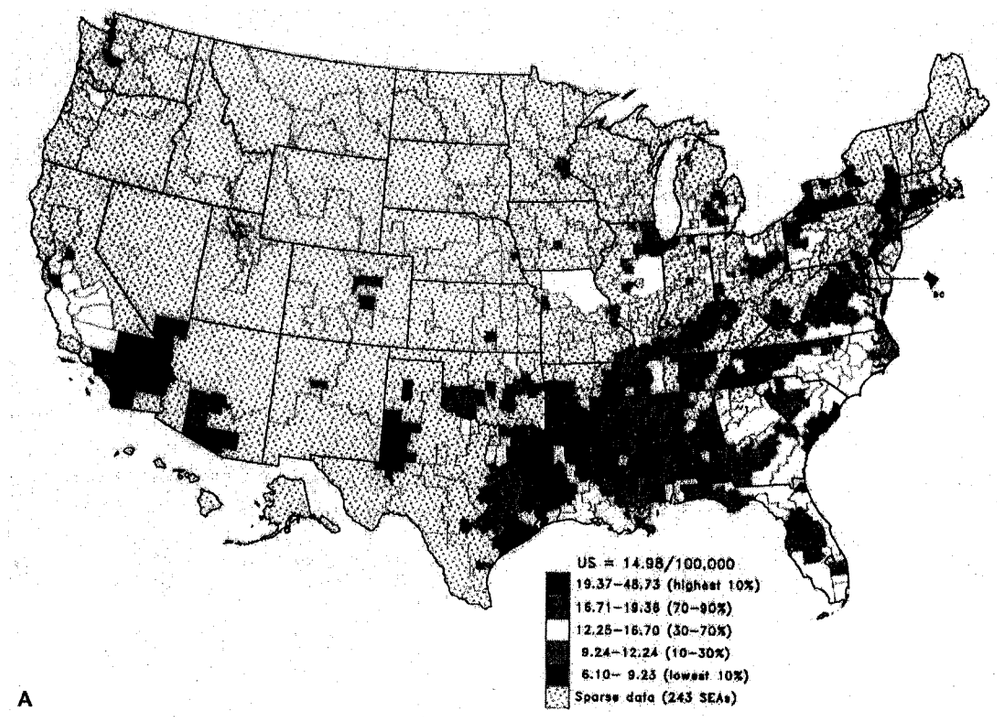


Figure 1–2. Cancer mortality rates for esophageal cancer by state economic area (SEA) (per 100,000 person-years, age-standardized to the 1970 US population) for white males (*A*) and females (*B*), from 1970 to 1994. (Data from the National Center for Health Statistics.)



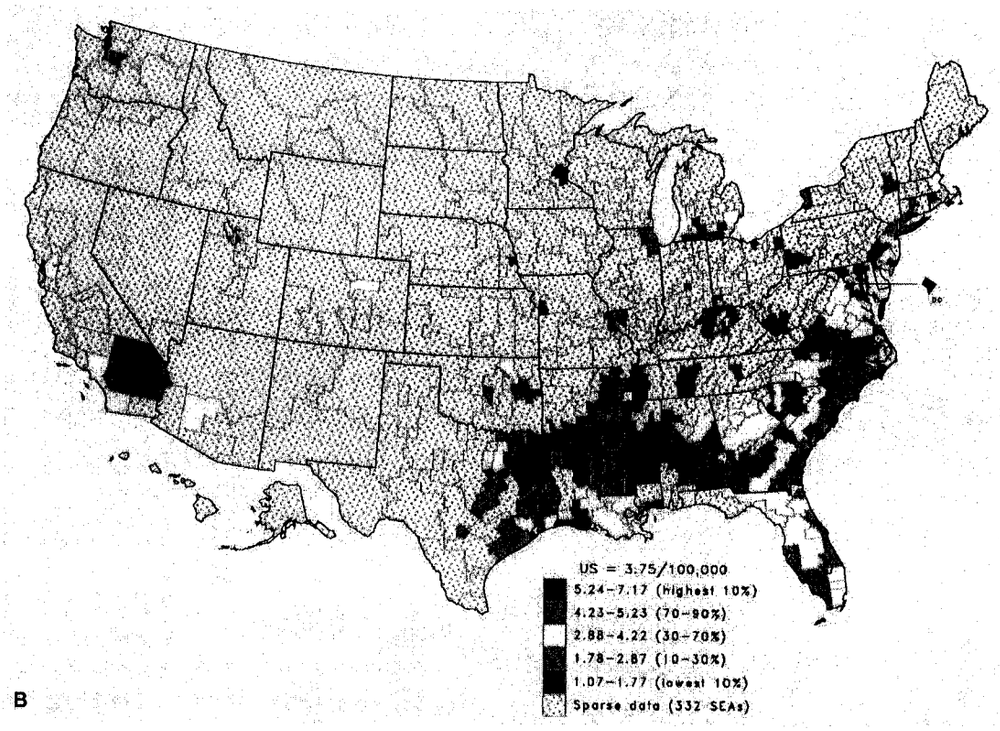


Figure 1–3. Cancer mortality rates for esophageal cancer by state economic area (SEA) (per 100,000 person-years, age-standardized to the 1970 US population) for African American males (*A*) and females (*B*), from 1970 to 1994. (Data from the National Center for Health Statistics.)

Table 1–1. ESOPHAGEAL CANCER 5-YEAR RELATIVE SURVIVAL RATES* BY DIAGNOSIS YEAR, GENDER, AND RACE

Year of Diagnosis	All Races			White			Black		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
1974–76	4.6	3.7	6.8	5.1	4.4	6.6	4.0	2.1	9.0
1977–79	5.0	4.7	5.8	5.6	5.6	5.6	2.8	2.4	4.3
1980–82	6.8	6.1	8.5	7.4	6.6	9.2	5.4	4.6	7.2
1983–85	8.3	7.0	11.8	9.3	7.8	13.1	6.3	5.2	9.5
1986–88	9.9	10.0	9.7	10.8	11.4	9.6	7.3	7.1	8.0
1989–95	12.3	12.1	13.1	13.3	13.2	13.6	8.9	8.0	10.7

*per 100,000.

Data from Surveillance, Epidemiology, and End Results (SEER), National Cancer Institute. Based on data from population-based registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound, and San Francisco–Oakland. Rates are based on follow-up of patients through 1996.

United States Incidence Patterns

As suggested by the relatively unfavorable survival rates, the incidence and mortality patterns for esophageal cancer are quite similar. Age-adjusted incidence rates for esophageal cancer among African American men peaked at 19.9 per 100,000 in 1985 to 1987 and then began a marked decline, reaching 13.3 per 100,000 in 1994 to 1996, whereas rates among white men increased steadily during the period of 1976 to 1996 with rates approaching 6.1 per 100,000 in 1994 to 1996 (Figure 1–4). Rates among white women changed little, but rates have declined among African American women since the mid-1980s. The dramatic decrease in total esophageal cancer rates for African American males was driven by the concurrent drop in rates for SCE. However, the SCE rate decreased after 1987 for all race and gender groups. Among white males, the incidence of ACE rose from 0.76 per 100,000 in 1976 to 1978 to 3.6 per 100,000 in 1994 to 1996, an increase of more than 350 percent. With the decrease in SCE and the increase in ACE, rates for ACE among white men have recently surpassed those for SCE. Rates of ACE among white females, although much lower than among white males, also increased more than 350 percent, from 0.12 per 100,000 in 1976 to 1978 to 0.44 per 100,000 in 1994 to 1996. In addition, ACE increased almost 200 percent among African American males, from 0.29 per 100,000 in 1976 to 1978 to 0.83 per 100,000 in 1994 to 1996; however, the rates of SCE remained considerably higher. Rates of ACE over the 21-year period varied more for African American females since the rates were based on only 34 cases. Decreases in the reported incidence of esophageal cancers not attributed to SCE or ACE were also seen over the 21-year time period. Even if some cases of ACE were previously misclassified as other or undefined histology, the small difference (0.25 per 100,000) between the rates for 1976 to 1978 and 1994 to 1996 could not account for the large increase among white males (2.8 per 100,000) observed between these two periods.

Table 1–2. ESOPHAGEAL CANCER SURVIVAL RATES BY STAGE CELL TYPE, AND STAGE DISTRIBUTION PERCENT, 1989 TO 1995

Stage	All Esophagus		Squamous Cell		Adenocarcinoma	
	Rate	Percent	Rate	Percent	Rate	Percent
All stages	12.3	100	11.7	100	13.5	100
Localized	24.9	24	20.1	28	34.1	23
Regional	12.7	25	12.6	26	12.1	27
Distant	1.9	25	2.3	22	1.6	30
Unstaged	10.5	25	10.2	25	10.1	19

Data from Surveillance, Epidemiology, and End Results (SEER), National Cancer Institute. Based on data from population-based registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound, and San Francisco–Oakland. Rates are based on follow-up of patients through 1996.
*per 100,000.

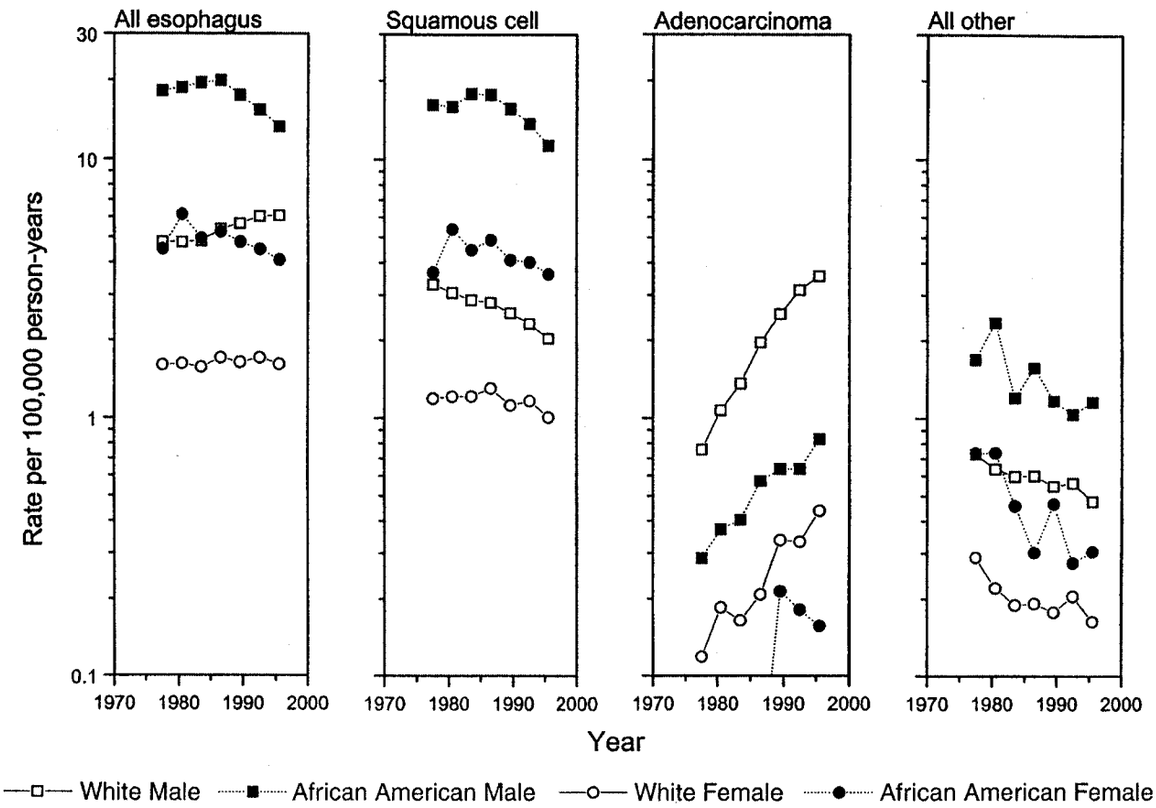


Figure 1–4. Trends in esophageal cancer incidence rates (per 100,000 person-years, age-standardized to the 1970 US population) in nine Surveillance, Epidemiology, and End Results (SEER) areas in the United States by cell type, race, and sex, 1976 to 1996. (Data from SEER program, National Cancer Institute.)

Figure 1–5 shows age-specific incidence rates for all esophageal cancers and for esophageal cancer by cell type, for 1990 to 1996. For all esophageal cancers among adults (age ≥ 25 years), rates were highest among African American males and lowest for white females at all but the highest ages. At ages 35 to 54 years, rates for African American females exceeded those for white males, but among individuals 55 years of age and older, the rates for white males surpassed those for African American females. Among white Americans, incidence rates rose steadily with age for females whereas they increased and then plateaued for men aged 75 years or more. Among African Americans, incidence rose until age 74 years and then decreased for both men and women. The rates of SCE were considerably higher among African American than among white men at all ages whereas rates for African American females exceeded those for white men, except for the oldest age group. For ACE, rates at all ages were highest among white males and generally lowest among African American females although the rates among African American females were less stable due to the small number of cases. Rates for African American males surpassed those for white females of all ages except those aged 85 years and older. Rates rose with age for white females and for African American and white men except for the most elderly. Rates for esophageal cancer of other cell types (including the unspecified category) rose consistently with age, were substantially higher at all ages in men than in women, and were generally higher in African American men than in white men.

Based on incidence data from the SEER program, 1990 to 1996, the overall rates for esophageal cancer varied from a high of 4.8 per 100,000 in Detroit to a low of 2.0 per 100,000 in Utah (Table 1–3). There was also considerable variation in the African American

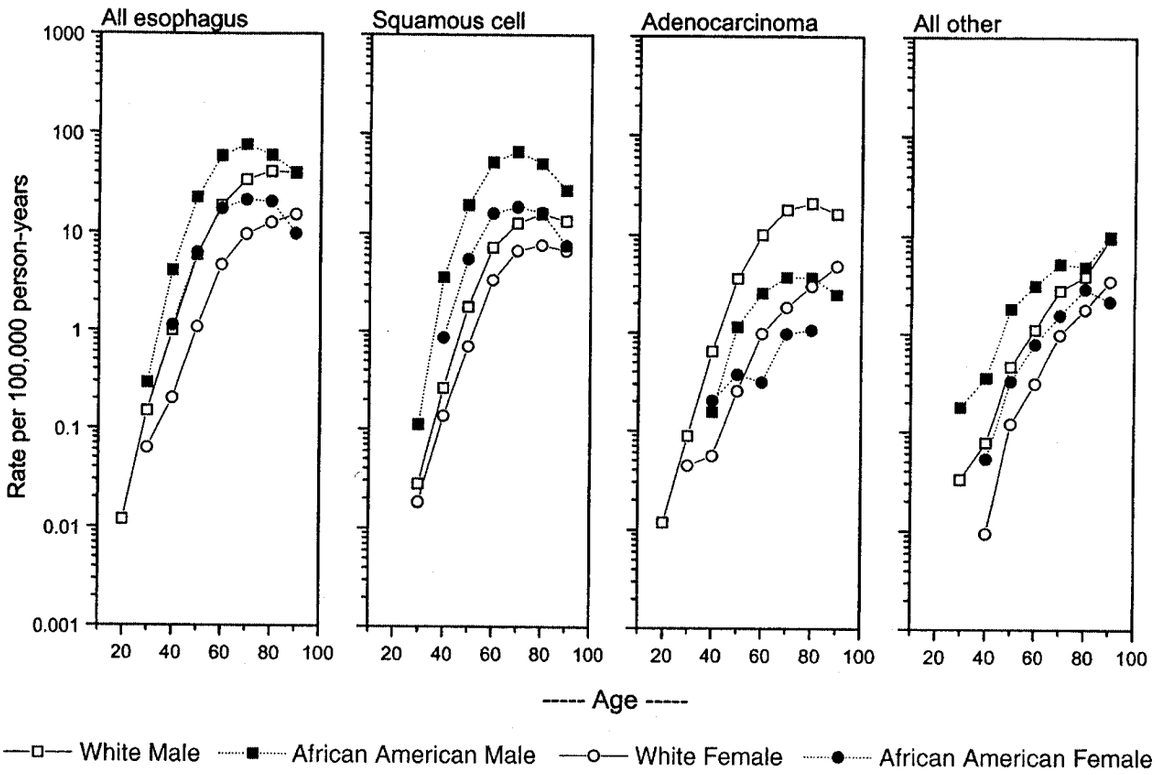


Figure 1–5. Age-specific esophageal cancer incidence rates in nine Surveillance, Epidemiology, and End Results (SEER) program areas in the United States by cell type, race, and sex, 1990 to 1996. (Data from SEER program, National Cancer Institute.)

rate/white rate ratio, ranging from 3.2 in Detroit and Atlanta to only 1.1 in Hawaii. (No cases among African Americans were reported in Utah.) Dramatic differences were seen, according to cell type. For SCE, the rates were highest among African Americans in Connecticut (11.2 per 100,000) and lowest among whites in Utah (0.7 per 100,000). For ACE, the highest rate was 2.1 per 100,000, among whites in Seattle, whereas the lowest was 0.3 per 100,000, among African Americans in San Francisco–Oakland and in

Table 1–3. AGE-ADJUSTED ESOPHAGEAL CANCER INCIDENCE RATES,* 1990 TO 1996, BY RACE AND CELL TYPE

Registry	All Esophagus			Squamous Cell			Adenocarcinoma		
	Total	White	Afr Am	Total	White	Afr Am	Total	White	Afr Am
All 9 SEER registries	4.0	3.6	9.0	2.2	1.6	7.9	1.5	1.7	0.4
San Francisco–Oakland	4.0	3.8	7.3	2.2	1.7	6.6	1.4	1.8	0.3
Connecticut	4.5	4.0	12.8	2.5	2.0	11.2	1.7	1.7	0.7
Detroit (Metropolitan)	4.8	3.8	9.1	3.0	1.7	7.8	1.4	1.6	0.5
Hawaii	3.1	4.0	4.4	2.4	2.9	4.4	0.5	0.7	0.0
Iowa	3.4	4.0	6.1	1.3	1.3	5.2	1.8	1.8	0.9
New Mexico	2.9	3.0	5.0	1.3	1.2	3.9	1.2	1.3	0.0
Seattle (Puget Sound)	4.3	4.4	5.4	2.0	1.9	4.8	2.0	2.1	0.3
Utah	2.0	2.0	0.0	0.7	0.7	0.0	1.1	1.1	0.0
Atlanta (Metropolitan)	4.6	3.1	9.9	3.1	1.4	8.9	1.1	1.3	0.4

Afr Am = African American; SEER = Surveillance, Epidemiology, and End Results.
*Rates per 100,000 person-years, age-adjusted using 1970 US standard, from nine Surveillance, Epidemiology, and End Results (SEER) program areas.
Data from SEER, National Cancer Institute.

Seattle. (No cases of ACE were reported among African Americans in Hawaii, New Mexico, or Utah.)

The overall incidence rates for esophageal cancer among males and females combined in the nine SEER registries were more than two times greater among African Americans (8.2 per 100,000) than among white Americans (3.5 per 100,000) (Table 1–4). Although based on small numbers, rates among Hispanics, Asians and Pacific Islanders, and Native Americans were lower than those among whites.

International Patterns

International differences in esophageal cancer incidence rates from 1988 to 1992 are dramatic[4] and largely reflect the geographic variations in the incidence of SCE. Published rates among males were highest in Calvados, France (22.3 per 100,000, followed by rates in Hong Kong and in Miyagi, Japan), and lowest in Israel (1.7 per 100,000) (Figure 1–6). However, the highest rates in the world have occurred in parts of China and Iran, which are not covered by population-based tumor registries. Among females, the rates ranged from 8.3 per 100,000 in Bombay, India, to 0.2 per 100,000 in Tarragona, Spain. Rates for African Americans ranked among the highest whereas those for white Americans were among the lowest. Internationally, the male/female rate ratio has varied from less than 1.4 to more than 20. The upward trend in ACE incidence seen in the United States has been reported in several countries in Europe.[5–13]

Table 1–4. AGE-ADJUSTED ESOPHAGEAL CANCER INCIDENCE RATES,* 1990–1996, BY RACE/ETHNICITY AND GENDER

Race/Ethnicity	Rate per 100,000 Persons		
	Total	Males	Females
All races	3.8	6.3	1.8
White	3.5	5.7	1.6
White Hispanic	2.5	4.7	—
White non-Hispanic	3.6	5.8	1.7
African American	8.2	13.5	4.2
Asian/Pacific Islander	2.5	4.5	0.8
Native American	1.3	2.5	0.4
Hispanic	2.4	4.4	—

*Rates per 100,000 person-years, age-adjusted using 1970 US standard. Data from Surveillance, Epidemiology, and End Results (SEER), National Cancer Institute. Based on data from population-based registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound, and San Francisco–Oakland.

ETIOLOGIC FACTORS FOR SQUAMOUS CELL CARCINOMA

Alcohol Consumption

Although attempts to produce cancer in well-nourished laboratory animals by prolonged ingestion of ethanol have failed,[14] there are clear-cut epidemiologic data indicating that alcoholic beverages are a major cause of SCE in Western populations.[15,16] The evidence is based on a number of cohort studies among alcoholics and heavy consumers of alcohol as well as case-control studies around the world.[15,17] For example, the incidence of esophageal cancer was significantly elevated among a cohort of alcoholic men and women attending an outpatient clinic in Denmark[18] and among a population-based cohort of Swedish men and women with a discharge diagnosis of alcoholism.[19] Furthermore, strong dose-response relationships for ethanol consumption have been demonstrated in many case-control studies in the United States, Europe, South America, Asia, and South Africa, after adjustment for smoking.[20–36] The percentage of SCE attributable to intake of more than one drink of alcohol a day in the United States has recently been estimated at 77 percent for white men and 82 percent for African American men.[37]

In some developing countries with exceptionally high rates of SCE, including rural parts of Africa, Iran, and China, alcohol drinking has not been shown to be a risk factor.[38–45] However, a strong dose-response relationship has been reported among Hong Kong Chinese,[31] in Shanghai, China (an urban area with high rates of esophageal cancer), and in Heilongjiang Province, a low-risk area in northern China.[30,46] Alcohol also recently emerged as a risk factor in southern India although only 36 percent of the cases and 14 percent of the controls reported drinking alcoholic beverages.[47]

Only a few studies of alcohol-related esophageal cancer have investigated covariables such as risk in nonsmokers and duration of use. In Italy, Hong Kong, and South America, the dose-response gradients for alcohol consumption remained strong when analyses were restricted to lifelong nonsmokers.[28,48–50] Other measures of exposure, such as duration and the age at which an individual started drinking alcohol, have not shown significant risk gradients

in case-control studies in France, Hong Kong, Paraguay, and Argentina.[29,32,35,51] Years elapsed since cessation of drinking alcohol did not affect the risk of esophageal cancer in France or Argentina[35,51] but did in Hong Kong and Paraguay, after investigators excluded an elevated risk among those who had recently quit drinking (probably due to early symptoms of cancer).[29,32]

Risk variability by type of alcoholic beverage may reflect culturally or economically determined drinking habits. Generally, the beverage most strongly associated with the risk of esophageal cancer has been the one most frequently consumed by the study population.[25,26,52] In most studies, the risk was greatest among users of "hard" liquor[20,21,23,24] although one study suggested a reduced risk in three regions of France.[26] Beer consumption was a key determinant of risk in several studies[26,53,54] whereas wine consumption was most strongly implicated in a region of Italy where wine is the major contributor to ethanol intake.[52] A study of esophageal cancer in a high-risk area of coastal South Carolina revealed an elevated risk associated with use of moonshine (home-brewed whiskey), particularly among African Americans,[20] further suggesting that regional variation in the type of alcoholic beverage consumed may contribute to the excess risk in some areas. Consumption of apple brandy in France, home-brewed rum in

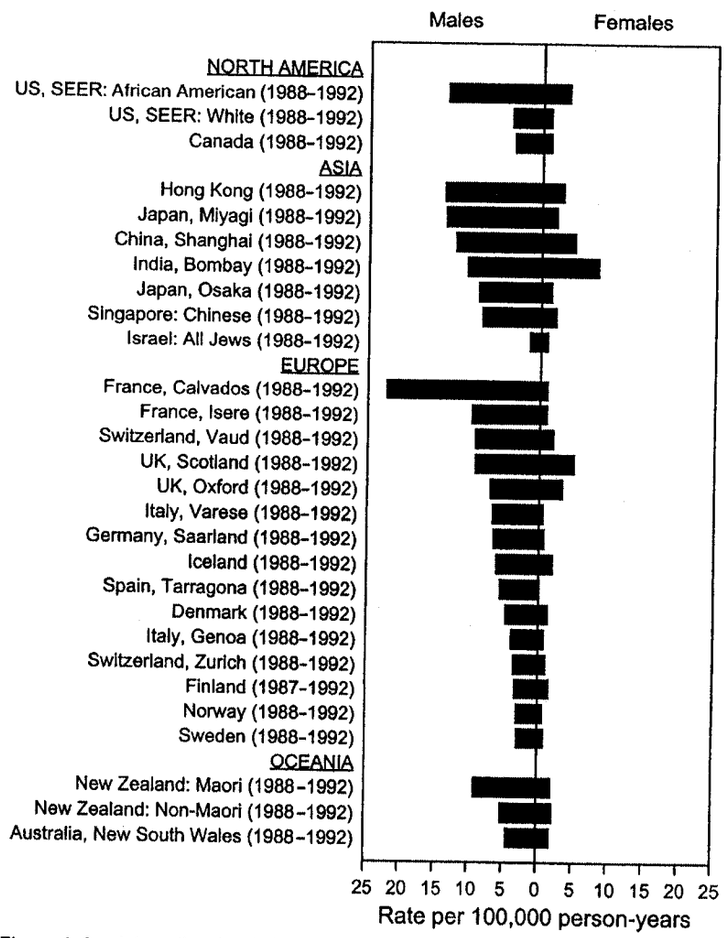


Figure 1–6. International variation in esophageal cancer incidence rates (per 100,000 person-years, age-standardized to the world population) by continent, registry, and sex, circa 1988 to 1992. (SEER = Surveillance, Epidemiology, and End Results.) (Adapted from Parkin DM, Whelan SL, Ferlay J, et al. Cancer incidence in five continents. Vol. VII. Lyon: International Agency for Research on Cancer; 2000.)

Puerto Rico, and aguardiente (a local spirit) in Paraguay has been associated with an excess risk of esophageal cancer in these countries, where these beverages are commonly used.[32,55,56] In Japan, shochu (the beverage with the highest alcohol content) was associated with the greatest risk of esophageal cancer.[27] Consumption of hot alcoholic beverages, especially hot calvados, was associated with elevated risks of esophageal cancer in France whereas the intake of cold calvados was not, suggesting a role for thermal injury to the esophagus.[26] It was suggested that the formerly widespread habit of drinking hot calvados contributed to the geographic variation of esophageal cancer and to the recent downward trend in incidence in western France.[26,57]

Although alcohol is strongly related to risk of esophageal cancer, the components or mechanisms responsible for its carcinogenicity have not been identified. Some studies have reported an excess risk for men who drink undiluted liquor (instead of liquor diluted with water, ice, or a mixer)[16,21,58] and have reported drinking dark liquor poses no more risk than drinking light liquor.[16] While certain kinds of alcoholic beverages, including beer and whiskey, may contain compounds that are carcinogenic, such findings suggest that the risk of SCE is associated with alcohol per se rather than to the presence of contaminants, flavoring compounds, or additives that may vary among types of beverages.[15] Alcohol itself may enhance cancer development by acting as a chronic irritant or by promoting dietary deficiencies.[26,59,60] It may also enhance an individual's susceptibility to tobacco or other carcinogens through a variety of mechanisms (eg, by interfering with deoxyribonucleic acid [DNA] repair mechanisms, altering the immune system or metabolic pathways, increasing absorption, or enhancing the activation of procarcinogens).[59,60] A recent study from Japan suggests that acetaldehyde, a metabolite of alcohol and a recognized animal carcinogen, may play a critical role in the mechanism by which alcohol causes esophageal cancer.[61] In this study, a significantly higher frequency of the mutant acetaldehyde dehydrogenase 2 (ALDH2*2) allele that blocks the metabolism of acetaldehyde to acetate was found in cancer patients than in controls with similar levels of alcohol consumption.[61]

Tobacco Consumption

Tobacco use, regardless of form, is a major risk factor for esophageal cancer in most parts of the world.[16,20,23,28,31,33,38,40,51,62–64] In the United States, the percentage of SCE attributable to the smoking of any form of tobacco (in cigarettes, cigars, or pipes) for 6 months or longer has recently been estimated at 65 percent for white men and 57 percent for African American men.[37] A case-control study in a high-risk area of Shanxi Province, China, did not find a significant association with tobacco use, but the amount of tobacco used (< one cigarette per day, on average) was too small to show consistent results.[44] However, in urban Shanghai, where 70 percent of the male patients smoked 20 or more cigarettes per day, there was a strong and significant association with cigarette smoking.[46] Significant positive trends in risk were associated with the intensity, duration, and number of packs per year times number of years smoked.[46] A significant association between esophageal cancer and the intensity of cigarette smoking was also noted in an area in northeast China with a relatively low incidence[30] but not in southern India, where only 4 percent of the case patients and 8 percent of the controls reported smoking only cigarettes.[47]

In some studies, pipe smokers have shown a higher risk of esophageal cancer than smokers of commercial cigarettes,[20,23,24,36,62] perhaps because pipe tobacco condensates are swallowed, allowing tobacco carcinogens direct contact with the esophagus.[62] A number of known or suspected carcinogens such as nitrosamines, 2-naphthylamine, benzo[*a*]pyrene, and benzene have been identified in tobacco smoke condensate,[65] but the specific agents responsible for esophageal cancer and mechanisms of action are unclear.[66]

Several case-control studies have reported strong positive dose-response effects with both duration and intensity of cigarette smoking[20,25,32,34] although duration of use seemed more important in some studies.[28,34,51] In most studies evaluating the effect of quitting smoking, a 50 percent reduction in risk has been seen for ex-smokers compared to current smokers,[20,23,28,33,34,51] along with an inverse effect with time elapsed since cessation of smoking.[20,25,32,34] The risk for those who quit smoking for 10 or more years

was similar to the risk for nonsmokers in South Carolina[20] whereas the risk for ex-smokers in Paraguay and California remained elevated even among smokers who had quit for 20 or more years. Smoking was also significantly related to esophageal cancer risk among nondrinkers in Italy, France, and Hong Kong,[49,50,64] supporting an independent effect of tobacco smoke on the esophageal epithelium.[64]

In several studies from South America, the risks of esophageal cancer from the use of black (air-cured) tobacco were two or more times higher than those for blond (flue-cured) tobacco.[25,35,67] Laboratory studies have indicated that the smoke of black tobacco contains higher levels of aromatic amines and tobacco-specific nitrosamines than the smoke of blond tobacco.[67] In addition, the urine of smokers of black tobacco shows twice the mutagenic activity of the urine of smokers of blond tobacco.[68] In several studies, risks were higher with hand-rolled cigarettes than with commercial cigarettes.[25,30,36,62,67] Although the carcinogenic ingredients are not clearly known, hand-rolled cigarettes have a high tar content and usually contain black tobacco.[67]

A case-control study in Bombay, India, identified the smoking of bidi (native cigarettes of coarse tobacco in a dry termburni leaf), the chewing of pan (a mixture of betel leaf, sliced areca nut, and aqueous shell lime), and the chewing of pan-tobacco (pan plus natively cured dry tobacco) as major risk factors for esophageal cancer.[69] A study in southern India found elevated risks for bidi and for bidi plus cigarettes but not for pan plus chewing tobacco, possibly due to the local habit of spitting out the quid and its extracts with the saliva rather than swallowing it.[47]

Alcohol-Tobacco Interaction

In western Europe and North America, 80 to 90 percent of the risk of SCE has been attributed to alcohol and tobacco use.[70] Alcohol and tobacco appear to act independently, with the importance of each factor depending on the baseline characteristics of the population under study.[71] In a population with a high percentage of heavy drinkers, the major factor appears to be alcohol[72] whereas tobacco seems more important in a population with many heavy smokers.[24,71] In most studies, heavy consumers of both alcohol and tobacco have the highest risk of esophageal cancer, often consistent with multiplicative interaction.[25,28,30,33–35,46,46,73]

Socioeconomic Status

The highest rates of SCE are generally found in areas of the world where the population is impoverished.[74] Within various populations, the risk of esophageal cancer is greatest among those with the lowest socioeconomic status (SES).[30,38,45,75–81] The measures of SES that are assessed most often in case-control studies are income, education, and occupation.

Income was the social-class variable most strongly associated with SCE in a case-control study conducted among African American and white men in three areas of the United States.[37] Significantly elevated risks of 4.3 for whites and 8.0 for African Americans were observed for the lowest versus the highest level of annual income, after adjusting for potential confounding factors such as smoking and drinking.[37] An association with low income has been noted in other studies in the United States and China,[39,76,82,83] risks are especially high for subjects whose incomes are at or below the poverty level.[37,79] Elevated risks of esophageal cancer have also been associated with low levels of education[21,26,45,75,77,81,84–86] and low-status occupations.[38,77,81] In addition, increased risks have been reported for single men in comparison to married men,[26,36,77,78,81,83,87] a finding that was stronger in the United States for African American than for white men.[37]

Low SES is obviously a surrogate for a set of lifestyle and other environmental factors, such as poor housing, unemployment, workplace hazards, limited access to medical care, stress, poor nutrition, and exposure to infectious agents.[82] Some of these factors, such as nutritional status, may affect an individual's susceptibility to environmental carcinogens.[88,89] For example, the number of esophageal cancers among male residents of hostels for single homeless people in Glasgow, Scotland, was considerably higher than expected. The finding is probably related not solely to alcohol abuse or smoking but also to the complex social problems of poverty, nutritional deficiencies, poor living conditions, and homelessness.[90]

Diet and Nutrition

Food Groups and Nutrients

A number of studies have indicated that dietary insufficiencies contribute to the varying incidence of SCE around the world.[91–94] Populations at high risk for this tumor are generally malnourished, and risk tends to increase as body mass index (BMI) decreases.[20,72,95–97] Until recently, esophageal cancer was unusually common in women from the rural northern areas of Sweden, many of whom had Plummer-Vinson syndrome, which is associated with vitamin and iron deficiencies.[98] Esophageal cancer has also been reported as a sequel of celiac disease, a malabsorption syndrome characterized by malnutrition.[99,100]

A protective effect of fruits and vegetables, especially those eaten raw, is supported by a large quantity of data, including data from case-control studies of esophageal cancer in Europe,[63,101–103] Asia,[30,31,33,39,49,84] North America,[20,22,23,53,72,97] and South America.[25,104] Fruits and vegetables contain a variety of micronutrients and other dietary components (eg, carotenoids; vitamins A, C, and E; selenium; fiber; indoles; and isothiocyanates) with potential anticarcinogenic effects.[105–107] A number of case-control studies have suggested a protective effect of vitamin C from supplements and food sources[20,30,72,84,97,108–110] and especially from fruits and citrus fruits. Vitamin C blocks the endogenous formation of *N*-nitroso compounds, which are suspected in the etiology of esophageal cancer in some high-risk areas of the world.[111–114]

Case-control studies have attempted to evaluate other food groups and nutrients, but the evidence is less convincing.[92] Although early studies examined the risk associated with total vitamin A intake, recent case-control studies suggested that an elevated risk is associated with high consumption of retinol-containing foods such as liver[20,101,102] whereas carotene appears to be either protective or unrelated to risk.[20,53,63,101,102,115]

Elevated risks associated with other animal sources of food (especially barbecued or fried meats) have been noted in some case-control studies of esophageal cancer.[20,23,25,32,35,53,72,101,103,116] Heterocyclic amines are potent mutagens and carcinogens formed during the cooking of meat, and their levels increase with rising temperature and duration of cooking (particularly with red meats), with the highest mutagenic activity being produced by pan frying, broiling, and barbecuing.[117] In addition, the higher risks associated with red meat (especially cured or processed meat) as well as with moldy breads and cereals, pickled vegetables, and salted fish suggest an effect of *N*-nitroso compounds or their precursors (nitrates and amines).[31,39,44,49,85,111–113,116,118] Furthermore, the endogenous formation of *N*-nitroso compounds may contribute to the development of esophageal tumors, particularly when accompanied by low intake of vitamins C and E, which interfere with the nitrosation process.[114]

A protective effect of the frequent consumption of fresh fish has been reported in two European case-control studies.[103,119] Fish and fish oils contain polyunsaturated omega-3 essential fatty acids that may reduce cancer risk by suppressing cell growth and proliferation or by enhancing apoptosis.[120]

It has been difficult to disentangle the influence of dietary and nutritional factors from the potent effects of alcohol and tobacco on the risk of esophageal cancer. In particular, heavy consumption of alcoholic beverages can interfere with the consumption and use of a variety of nutrients, including the B vitamins, zinc, protein, and vitamins A, C, and D.[59,60] Also, because poor nutrition is a risk factor for esophageal cancer, it is conceivable that alcohol increases risk partly by reducing nutrient intake. Beer, wine, and hard liquor provide a share of the daily caloric needs and consequently reduce appetite, but they provide almost none of the daily requirements for micronutrients and protein. Not only do smokers appear to have a lower intake of several nutrients (including vitamin C) than do nonsmokers,[121,122] but the amount of vitamin C needed to achieve steady-state plasma concentrations is approximately 40 percent greater in smokers than in nonsmokers.[123] In addition, tobacco products and some alcoholic beverages are sources of *N*-nitroso compounds that may elevate the risk of esophageal cancer.[111]

Hot Food and Beverages

It has been hypothesized that the consumption of herbal teas that are high in tannin, safrole, or other

agents might be responsible for the elevated rates of esophageal cancer in residents of coastal South Carolina.[124] While a study in South Carolina found that several herbal teas were commonly used, intake was generally not more frequent in case subjects than in controls,[20] so that consumption of herbal teas or local plant products is unlikely to explain the high rates in this area. Several studies have suggested that drinking tea at normal temperatures does not increase risk.[20,125–127] In fact, consumption of green tea at normal temperatures was associated with a reduced risk of esophageal cancer in a large case-control study in Shanghai and in a high-risk area in Jiangsu Province, China.[39,126]

However, drinking tea at exceptionally high temperatures (including green tea, as found in a Japanese study[33]) has long been suggested as a risk factor in several populations.[92,128] The findings are consistent with the excess risks associated with the consumption of burning hot soup, gruel, porridge, or other beverages in various populations.[27,30,31,42,44,84,104] In high-risk areas of South America, chronic thermal injury from maté, a local tea prepared as an infusion of the herb *Ilex paraguayenis* and usually drunk very hot, has been linked to esophageal cancer.[25,32,35,104] Because most people either drink hot maté or drink both hot and cold maté,[32] it has been difficult to determine whether the effects are due to specific components of maté, to the elevated temperature, or to both factors.[32,92] However, a study in Paraguay revealed a significant twofold risk for the consumption of very hot maté compared to hot or warm maté,[32] and a study in Argentina found an elevated risk for the consumption of hot or very hot maté compared to warm maté.[35] Based on the South American data, a working group of the International Agency for Research on Cancer concluded in 1991 that "hot maté drinking is probably carcinogenic to humans."[129]

Occupation and Industry

Esophageal cancer is not usually viewed as an occupational disease although elevated risks have been reported for several exposures. Most findings have come from occupational cohort studies although some findings have emerged from case-control studies. Because most studies were unable to adjust for the confounding effects of smoking and drinking, the results of occupational analyses are often equivocal. Presented below are some of the more consistent findings.

Occupational Risks Due to Lifestyle Factors

Farmers are usually considered to have a healthier lifestyle than the general population.[130] The lower risks of esophageal cancer reported among farmers in Sweden and Denmark seemed related to their lower intake of alcohol[130–133] although the elevated risks among Italian farmers may have resulted from a higher consumption of alcohol compared to that of the general population.[132] Excess risks reported among Swedish brewery workers[133,134] and among Norwegian and Swedish waiters[133,135] appeared to be due to a higher intake of alcohol in these groups.

Perchloroethylene

The most consistent occupational association with esophageal cancer has been the excess risk among dry cleaners and other occupational groups (eg, metal polishers and platers) exposed to perchloroethylene (PCE),[136–139] a substance used by the dry cleaning industry as a cleaner and by other industries as a degreaser and solvent.[138] Cohort studies among dry cleaning union members by the National Cancer Institute and the National Institute for Occupational Safety and Health have revealed twofold excesses in esophageal cancer mortality. In addition, a modest excess of esophageal cancer, which could not be explained by the use of alcohol or cigarettes, was observed among dry cleaning workers in a case-control study in Washington state.[137] An excess of esophageal cancer mortality has also been noted among metal polishers and platers.[139]

Combustion Products and Fossil Fuels

Esophageal cancer may be caused by exposure to fumes from incomplete combustion of organic material; increased risks have been observed for chimney sweeps, printers, gas station attendants, vulcanization workers, asphalt workers, and metal workers exposed to metalworking fluids.[140] An excess risk

was observed in a Swedish cohort of chimney sweeps exposed to a mixture of polycyclic aromatic hydrocarbons (PAHs), nitrogen compounds, arsenic, asbestos, and sulfur dioxide.[141] Although a proportionate mortality study among workers at the US Government Printing Office observed no excess risk of esophageal cancer,[142] elevated risks have been reported in the printing industry in Russia and France, notably among bookbinders potentially exposed to benzene and among pressmen exposed to PAHs.[143,144] An excess risk of esophageal cancer was also reported among automobile manufacturing workers exposed to metalworking fluid.[145] In a cohort of filling station managers, the number of esophageal cancers was greater than expected for managers of small stations, possibly due to greater exposure to gasoline vapors and exhausts.[146] Elevated risks also have been observed in the rubber industry,[147,148] particularly among vulcanization workers[133,149] who are potentially exposed to PAHs, styrene, toluene, ethylbenzene, acrylonitrile, and vinyl chloride.[150,151] In addition, a significantly high risk of esophageal cancers was observed in a cohort of mastic asphalt workers heavily exposed to bitumen fumes.[152]

Silica and Metal Dust

Ingested silica and metal dust particles cleared from the lungs may damage the esophageal mucosa and promote cell proliferation.[23,153] Occupational exposure to silica dust at a large iron-steel complex in China was associated with a significant 2.8-fold risk and a strong positive gradient in risk with increasing duration of exposure.[153] This finding confirms the results of an earlier study that reported an elevated proportionate mortality ratio among workers at the iron-steel complex who made fire-resistant silica bricks.[154] An association with silica exposure was also noted in a recent study based on death-certificate data on occupation and industry from 24 US states.[155] In addition, a population-based case-control study of esophageal cancer in the United States found a significant association with occupational exposure to metal dust, especially from beryllium.[23] However, a nested case-control study among US automobile-manufacturing workers exposed to metal dust from iron and steel operations reported no excess risks.[145]

Asbestos

Increased risks of esophageal cancer have been reported among asbestos insulation workers in the United States and Canada.[156] However, no excess risk was reported among workers who had potential exposure to asbestos at Texas refineries and at a petrochemical plant.[157,158] Because of the inconsistent results, the relationship between asbestos exposure and esophageal cancer remains unclear.

Meat Packing and Slaughtering: Viral Exposure

Butchers and other workers employed in meat packing and meat slaughtering have shown elevated risks of esophageal cancer, suggesting a possible effect of exposure to bovine and human papillomaviruses.[133]

Other Risk Factors

A number of studies have linked ionizing radiation to esophageal cancer, particularly among patients irradiated for ankylosing spondylitis and for breast cancer.[159,160] In addition, significant excesses of risk have been reported among atomic-bomb survivors in Japan.[161]

Constituents of drinking water have been suspected in some studies of esophageal cancer. In Shanghai, China, excess risks have been related to the drinking of river water found to be mutagenic by the Ames test.[85] Similarly, water contaminated with petroleum and its by-products has been suspected in a high-risk area of Saudi Arabia.[162] On the other hand, high nitrate levels in drinking water were not related to esophageal cancer risk in northern England.[163]

Elevated risks of esophageal cancer have been reported with certain medical conditions (such as pernicious anemia,[164] achalasia,[165,166] some autoimmune diseases,[167] and chemical injuries to the esophagus)[168] and following gastrectomy.[169] In addition, aspirin use appeared to reduce the risk of esophageal cancer in cohort and case-control studies.[170,171] The ingestion of opium, either by smoking or eating, was linked to esophageal cancer in high-risk areas of Iran.[172]

The role of human papillomavirus (HPV) infection in the etiology of SCE is not entirely clear. Human papillomaviruses, especially types 16 and 18,[173] appear to play an etiologic role in some geographic areas, particularly regions with an exceptionally high incidence of esophageal cancer, such as China and South Africa,[3,174] but study results have not been consistent.[175,176]

Several studies in high-risk areas of Iran and China have indicated a familial tendency for esophageal cancer although it is difficult to distinguish genetic from environmental factors.[44,177,178] In clinical studies, a high risk of SCE has been reported in association with tylosis, a dominantly inherited disorder characterized by palmar and plantar keratoses.[173,179,180]

There is evidence that genetic polymorphisms (eg, ADH3, ADH2, CYP2E1) may increase susceptibility to SCE through interactions with alcohol, tobacco, and certain dietary components, [181,182] but more work is needed to confirm this. Several somatic mutations have been reported, including mutation of p53, a tumor-suppressor gene that promotes DNA repair, stimulates apoptosis, and inhibits cell proliferation.[183,184]

A striking excess risk of SCE has been demonstrated following the development of other tumors of the upper aerodigestive tract, including the oral cavity, pharynx, and larynx.[185,186] This constellation of multiple primary cancers is not surprising since alcohol and tobacco are the major risk factors for these tumors and since genetic mechanisms may also be shared.

Impact of Risk Factors in the United States

In a recent case-control study of SCE patients in three areas of the United States, moderate and heavy levels of alcohol intake, the use of tobacco, the infrequent consumption of raw fruits and vegetables, and low income were found to account for over 98 percent of the SCE among both African American and white men and for 99 percent of the excess incidence among African Americans compared to whites.[37] The higher incidence rates observed among African Americans after exposure to the same risk factors as whites may reflect a susceptibility state conditioned by genetic traits or by nutritional, viral, or other factors associated with low social class. Whatever the mechanism, it is clear that lifestyle modifications that include a reduction in the consumption of alcoholic beverages (especially among heavy drinkers) and in the use of tobacco, as well as improvements in diet and living conditions, would markedly lower the incidence of SCE in all racial and ethnic groups. Thus, it is likely that declines in the prevalence of smoking since the 1960s, especially among men, may have contributed to the downward trends reported for this cancer. However, recent increases in cigar smoking could negatively impact these trends.[187]

ETIOLOGIC FACTORS FOR ESOPHAGEAL ADENOCARCINOMAS

Tobacco Consumption

In the United States, cigarette smoking is a significant risk factor for ACE, with a doubling of risk for smokers of more than one pack a day.[96,188–190] Risks have been significantly elevated also for heavy smokers in China, Greece, and France[46,170,191] although smoking is a less potent cause of ACE than SCE. Unlike findings for SCE, being an ex-smoker does not appear to attenuate risks; instead, the risks remain elevated for more than 30 years after smoking cessation.[96,188,189,191] This finding suggests that smoking may affect an early stage of esophageal carcinogenesis and may thus still contribute to the rising incidence of ACE in the face of recent downward trends in smoking prevalence in the United States.[188]

Gastroesophageal Reflux Disease

A major risk factor is gastroesophageal reflux disease (GERD), which predisposes to the metaplastic columnar epithelium characteristic of Barrett's esophagus, a precursor lesion for ACE.[192,193] Significant twofold or greater risks of ACE have been associated with the presence of GERD symptoms.[189,194–196] It has been hypothesized that the use of drugs such as anticholinergic agents that relax the lower esophageal sphincter may promote GERD and thus contribute to the risk of ACE.[197] However, in two US case-control studies, the use of anticholiner-

gic drugs was not associated with risk of ACE.[194,198] Questions have also emerged about histamine H_2 receptor antagonists for treatment of GERD, but no clear relationship to ACE risk has been demonstrated. In evaluating the possible role of *Helicobacter pylori* infection, a case-control study in the United States found that infection with cagA+ strains was actually associated with a reduced risk of ACE.[199] Further investigations are needed to determine whether the decreasing prevalence of *H. pylori* infection in the population may contribute in some way to the upward trend of ACE.

Alcohol Consumption

While several case-control studies have suggested an association between alcohol intake and the risk of ACE, the risks are much lower than those seen with SCE.[96,189,190] In fact, no association with any measure of alcohol intake or type of beverage was noted in a large population-based case-control study in the United States.[188]

Socioeconomic Status

Low income has been related to excess risk of ACE in two US studies[188,189] although the effect is less pronounced than for SCE. This differential is consistent with studies reporting a higher percentage of ACE cases in people working in professional and skilled occupations, as compared with the percentage of SCE cases in such workers.[96,200,201]

Diet and Nutrition

In contrast to SCE, for which high-risk populations are generally poorly nourished, risks for ACE tend to increase as BMI increases:[95,96,190,194,202–204] subjects in the upper quartile of BMI have three to seven times the risk of subjects in the lowest quartile.[202–204] The mechanism by which obesity affects the risk of ACE is unclear although it may be linked to the predisposition of obese individuals to GERD.[190,202] Whatever the process, it seems likely that obesity contributes to the upward trend in ACE, in view of the sharply increasing prevalence of individuals classified as overweight in the United States.[205]

Various foods, food groups, and nutrients have been related to the risk of ACE, but the most consistent finding is a protective effect of fruits, vegetables, and fiber.[96,202,206] Fruits and vegetables contain various substances with potential anticarcinogenic effects,[106,109] and dietary fiber may have a mechanical cleansing or clearance action that removes or dilutes carcinogens from epithelial surfaces of the upper digestive tract.[207]

Genetic Susceptibility

Some case reports have suggested a familial tendency to Barrett's esophagus and ACE, [208,209] but further studies are needed to clarify the possible role of susceptibility genes.

Impact of Risk Factors in the United States

The incidence of ACE in the United States has been rising over the past couple of decades, especially among white men. Data emerging from recent studies suggest that the relationship with obesity and (possibly) smoking may account for part of the upward trend. Both smoking and obesity increase the incidence of GERD and its progression to Barrett's esophagus, the main precursor of ACE. The protective effects of fruits and vegetables and the modest effects of low SES are interesting but do not appear to explain the upward trends. In a case-control study in Seattle, only about half of the cases could be explained by known or suspected risk factors,[190] indicating the need for further epidemiologic and interdisciplinary research into the origins of this increasingly common cancer.

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